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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/296,031	04/21/1999	SUSAN A. LYONS PH.D.	D6218	7876

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	18

DATE MAILED: 05/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/296,031	LYONS PH.D. ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 4-15-02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/296,031 is acceptable and a CPA has been established. An action on the CPA follows.

The declaration by Dr. Matthew Gonda and amendment filed 4-15-02 have been entered. Claims 15-31 have been canceled. Claims 32-49 have been added. Claims 32-49 are pending and under consideration.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 32-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-9 of U.S. Patent No. 5,905,027. Although the conflicting claims are not identical, they are not patentably distinct from each other because, although drawn to different scope, they encompass the same invention and obvious variants thereof.

Claims 32-42 of the present application are drawn to a method of detecting a neuroectodermal tumor, such as glioma, meningioma etc., comprising contacting a patient tissue sample of interest with labeled chlorotoxin and the presence of chlorotoxin binding is indicative of the presence of the neuroectodermal tumor, wherein the chlorotoxin is labeled, such as a radiolabel and a fluorescent moiety, and the chlorotoxin label is detected by enzyme-linked immunosorbent assay, positron emission tomography scanning, fluorescent microscopy and fluorescent activated cell sorting. Claim 38 specifies the radiolabel is ^{3}H, ^{32}P, ^{35}S, and ^{125}I etc. Claim 41 specifies the fluorescent moiety is fluorescein, rhodamine etc.

Claims 3-9 of '027 are drawn to a method of differentiating glial-derived or meningioma-derived neoplastic tumor tissue from non-neoplastic tissue comprising contacting a tissue of interest with labeled chlorotoxin and an elevated level of chlorotoxin binding indicates the tissue is neoplastic, wherein the chlorotoxin is labeled with a fluorescent moiety. Claim 8 specifies the chlorotoxin binding is determined by fluorescent microscopy or fluorescent activated cell sorting (FACS). Claims 5, 6 and 9 specify the chlorotoxin is radiolabeled, such as ^{131}I-chlorotoxin or

^{125}I-chlorotoxin, and the radiolabeled chlorotoxin binding affinity is from 5 nM to about 5 uM determined by positron emission tomography scanning.

Neuroectodermal tumor encompasses Glial-derived or meningioma-derived neoplastic tumor. Differentiating a tumor tissue from a normal tissue is the same as detecting a tumor in a patient sample. It was known in the art to use fluorescein or rhodamine for fluorescent detection and to use enzyme-based immunoassay for calorimetric detection. Thus, it would have been obvious for one of ordinary skill at the time of the invention to practice the claimed invention according to the teachings of '027. Thus, claims 32-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-9 of U.S. Patent No. 5,905,027.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 33 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting neuroectodermal tumor such as glioma, glioblastoma, neuroblastoma etc, in a tissue sample by using chlorotoxin, does not reasonably provide enablement for detecting a peripheral primitive neuroectodermal tumors (PPNET) in a tissue sample by using chlorotoxin. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 33 is directed to a method of detecting a neuroectodermal tumor in a patient by contacting a patient tissue sample with chlorotoxin and the presence of chlorotoxin binding is indicative of the presence of neuroectodermal tumor, such as PPNET.

The specification only discloses the detection of glioblastoma, neuroblastoma, medulloblastoma, pheochromocytoma and metastatic melanoma etc. in a tissue sample by using chlorotoxin. The specification fails to provide evidence that there is chlorotoxin binding to PPNET and the presence of such binding is indicative of a PPNET in a tissue sample as compared to normal tissue. In fact, the specification indicates negative binding of chlorotoxin to PPNET tissue sample (see Table 1, page 42). In view of evidence of contrary in the specification, and lack of teaching in the art that there is clorotoxin binding to PPNET and such binding is indicative of the presence of PPNET, one skilled in the art at the time of the invention would not know whether chlorotoxin would bind to PPNET in a tissue sample and whether chlorotoxin binding would be indicative of the presence of PPNET. Thus, one skilled in the art would require undue experimentation to practice over the full scope of the invention claimed.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 32-49 are rejected under 35 U.S.C. 102(e) as anticipated by Ullrich et al., US Patent No. 5,905,027 (A) or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ullrich et al., US Patent No. 5,905,027 (A).

Claims 32-49 are drawn to a method of detecting a neuroectodermal tumor, such as glioma, meningioma etc., comprising contacting a patient tissue sample of interest with labeled chlorotoxin and the presence of chlorotoxin binding is indicative of the presence of the neuroectodermal tumor, wherein the chlorotoxin is labeled, such as a radiolabel, biotin and a fluorescent moiety, and the chlorotoxin label is detected by positron emission tomography scanning, fluorescent microscopy and fluorescent activated cell sorting. Claim 38 specifies the

radiolabel is ^{3}H, ^{32}P, ^{35}S, and ^{125}I etc. Claim 41 specifies the fluorescent moiety is fluorescein, rhodamine etc. Claims 46 and 47 specify the tissue is frozen or is embedded in paraffin. Claims 48 and 49 specify the tissue sample is counterstained with methyl green or hematoxylin and eosin.

Ullrich teaches a method of differentiating glial-derived or meningioma-derived neoplastic tumor tissue from non-neoplastic tissue comprising contacting a tissue of interest with labeled chlorotoxin and an elevated level of chlorotoxin binding indicates the tissue is neoplastic, wherein the chlorotoxin is labeled with a fluorescent moiety and the chlorotoxin binding is determined by fluorescent microscopy or fluorescent activated cell sorting (FACS). Ullrich also teaches that the chlorotoxin is radiolabeled, such as ^{131}I-chlorotoxin or ^{125}I-chlorotoxin, and the radiolabeled chlorotoxin binding affinity is from 5 nM to about 5 uM determined by positron emission tomography scanning (e.g. column 25, 26). Ullrich also teaches that chlorotoxin binding can be detected immunohistochemically by labeling GST-chlorotoxin fusion protein with DTAF (dichlorotriazinylaminofluorescein) and DTAF label can be visualized by direct immunofluorescence using standard FITC filters or by conjugating chlorotoxin with biotin that binds to avidin for subsequent recognition by antibodies or the reaction product (such as calorimetric product via enzymatic reaction) (e.g. column 22, 23).

It was known in the art to freeze tissue sample and embed tissue sample in paraffin for slicing the sample such that thin tissue section can be mounted on slide for subsequent immunohistochemical detection. It is also general knowledge to stain tissue section with

hematoxylin and eosin for visualization of the tissue section. Thus, claims 32-49 are rejected under 35 U.S.C. 102(e) as anticipated by Ullrich et al., US Patent No. 5,905,027 (A) or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ullrich et al., US Patent No. 5,905,027 (A).

9. Claims 32-35 and 37-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Sontheimer et al., 1997 (N).

Claims 32-35 and 37-44 are drawn to a method of detecting a neuroectodermal tumor, such as glioma, meningioma etc., comprising contacting a patient tissue sample of interest with labeled chlorotoxin and the presence of chlorotoxin binding is indicative of the presence of the neuroectodermal tumor, wherein the chlorotoxin is labeled, such as a radiolabel, biotin and a fluorescent moiety, and the chlorotoxin label is detected by positron emission tomography scanning, fluorescent microscopy and fluorescent activated cell sorting. Claim 38 specifies the radiolabel is ^{3}H, ^{32}P, ^{35}S, and ^{125}I etc. Claim 41 specifies the fluorescent moiety is fluorescein, rhodamine etc.

Sontheimer teaches a method of differentiating glial-derived or meningioma-derived neoplastic tumor tissue from non-neoplastic tissue comprising contacting a tissue of interest with labeled chlorotoxin and an elevated level of chlorotoxin binding indicates the tissue is neoplastic, wherein the chlorotoxin is labeled with a fluorescent moiety and the chlorotoxin binding is determined by fluorescent microscopy or fluorescent activated cell sorting (FACS). Sontheimer also teaches that the chlorotoxin is radiolabeled, such as ^{131}I-chlorotoxin or ^{125}I-chlorotoxin, and

the radiolabeled chlorotoxin binding affinity is from 5 nM to about 5 uM determined by positron emission tomography scanning (e.g. p. 54, 55). Sontheimer also teaches that chlorotoxin binding can be detected immunohistochemically by labeling GST-chlorotoxin fusion protein with DTAF (dichlorotriazinylaminofluorescein) and DTAF label can be visualized by direct immunofluorescence using standard FITC filters or by conjugating chlorotoxin with biotin that binds to avidin for subsequent recognition by antibodies or the reaction product (e.g. p. 46-49). Thus, claims 32-35 and 37-44 are anticipated by Sontheimer.

10. Claims 32-38 and 40-49 are rejected under 35 U.S.C. 102(a) as being anticipated by Soroceanu et al., 1998 (Cancer Research, Vol. 58, No. 21, p. 4871-4879).

Claims 32-38 and 40-49 are drawn to a method of detecting a neuroectodermal tumor, such as glioma, meningioma etc., comprising contacting a patient tissue sample of interest with labeled chlorotoxin and the presence of chlorotoxin binding is indicative of the presence of the neuroectodermal tumor, wherein the chlorotoxin is labeled, such as a radiolabel, biotin and a fluorescent moiety, and the chlorotoxin label is detected by fluorescent microscopy and fluorescent activated cell sorting. Claim 38 specifies the radiolabel is ^{3}H, ^{32}P, ^{35}S, and ^{125}I etc. Claim 41 specifies the fluorescent moiety is fluorescein, rhodamine etc. Claims 46 and 47 specify the tissue is frozen or is embedded in paraffin. Claims 48 and 49 specify the tissue sample is counterstained with methyl green or hematoxylin and eosin.

Soroceanu teaches preparation of biotinylated chlorotoxin (CTX) or fluorescent-tagged CTX for detection of CTX binding to glioma cells *in vitro* or *in vivo*. Cells were visualized with HRP-linked streptavidin conjugated with 3,3'-diaminobenzidine-peroxidase substrate or rhodamine conjugated streptavidin via epifluorescence or light microscope. Brain sections were embedded in OCT freezing medium and sectioned on a cryotome for detection of CTX binding via biotinylated CTX or fluorescent-tagged CTX set forth above, and the human tissue sections were counterstained with Mayer's hematoxylin (e.g. p. 4873). Soroceanu also teaches radiolabeling CTX with ^{125}I sodium iodide for *in vivo* CTX binding assay (e.g. p. 4872, right column). Soroceanu shows highly selective CTX staining of glioma cells *in vitro*, *in situ*, and in sections of patient biopsies but negative staining on normal human brain, kidney, and colon. Soroceanu suggests that "CTX anc CTX-conjugated molecules may serve as glioma-specific markers with diagnostic and therapeutic potential" (e.g. abstract). Thus, claims 32-38 and 40-49 are anticipated by Soroceanu.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.